Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 2011;364:1005-15.

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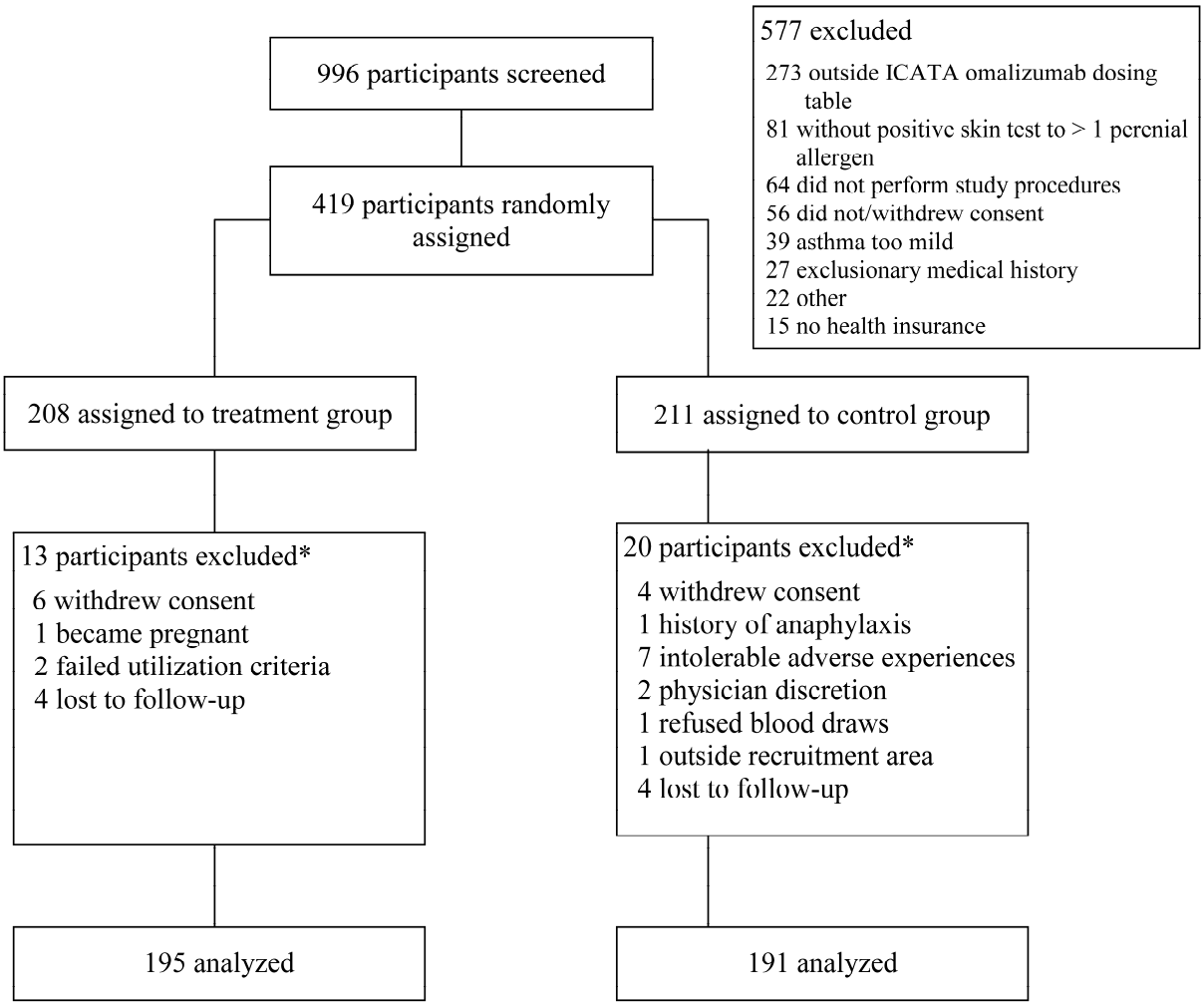
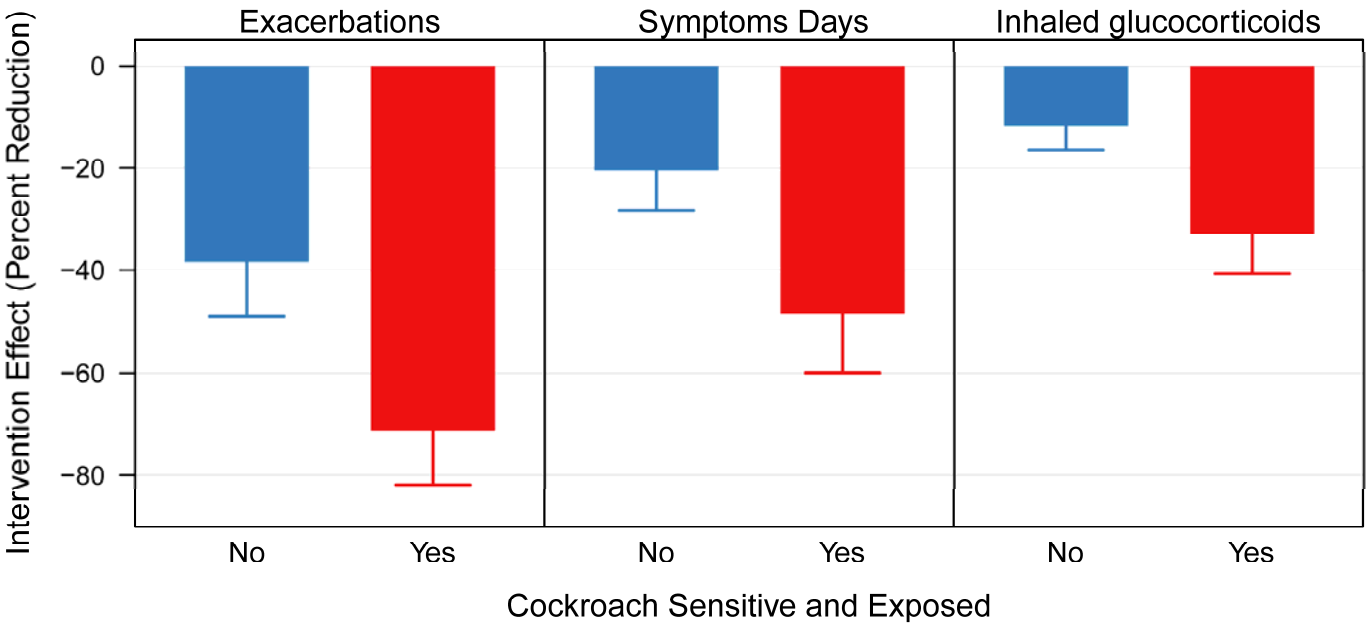
Supplement Appendix Figure 1: CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing the participants' course during the study



* These participants withdrew after random assignment but before the first outcome data were collected at week 12.

Supplement Appendix Figure 2: Omalizumab effect on participants sensitized and exposed to German cockroach.



Whiskers show standard errors. For statistically significance see Supplement Appendix Table 3

Supplement Appendix Table 1A: Control Levels of Symptoms, Bronchodilator Usage, and FEV1 (% personal best)

Control Level	Maximum of 1) # days with asthma symptoms/ two weeks and 2) # days with rescue albuterol use/ two weeks*	Maximum of 1) # nights of sleep disruption due to asthma/ two weeks and 2) # nights use of albuterol for awakening/ two weeks*	FEV_1 (% personal best)
1	0-3 days	0-1 night	≥ 85
2	4-9 days	2 nights	80-84
3	10-13 days	3-4 nights	70-79
4	14 days	5-14 nights	< 70
* Determined from participant recall, based on the 2-week interval directly preceding the study visit.			

Supplement Appendix Table 1B: Medication Treatment Steps

Step	Medication
0	No controller medication; albuterol prn
1	Budesonide DPI 180 mcg qd
2	Budesonide DPI 180 mcg bid
3	Budesonide DPI 360 mcg bid
4	Advair® 250 mcg/50 mcg bid
5	Advair® 250 mcg/50 mcg bid plus montelukast qd
6	Advair® 500 mcg/50 mcg bid plus montelukast qd

Supplement Appendix Table 1C: Treatment Adjustment Based on Control Levels and Adherence

Control Level	Treatment Algorithm for Participants with Unacceptable Adherence	Treatment Algorithm for Participants with Acceptable Adherence
1	Continue same controller regimen	If on Step 1, continue Step 1. If during open-label period, decrease controller regimen from Step 1 to Step 0. If on Steps 2-6, decrease controller regimen by 1 step.
2	Continue same controller regimen or place on Step 2 therapy, whichever is higher	Increase controller regimen by 1 step, or continue Step 6 therapy if already on Step 6.
3	Continue same controller regimen or place on Step 2 therapy, whichever is higher	If on Steps 1-4, increase controller regimen by 2 steps. If on Step 5, increase to Step 6. If already on Step 6, continue on Step 6.
4	Continue same controller regimen or place on Step 3 therapy, whichever is higher OR Treat with 4-day prednisone burst and continue same controller regimen or place on Step 3 therapy, whichever is higher	If on Steps 1-3, increase controller regimen by 3 steps OR treat with 4-day prednisone burst and increase controller regimen by 2 steps. If on Steps 4-5, increase to Step 6 OR treat with Step 6 and a 4-day prednisone burst. If already on Step 6, continue on Step 6 OR treat with Step 6 and a 4-day prednisone burst.

Supplement Appendix Table 2: Omalizumab Dosing Table

		Milligrams of Xolair Required per Dose									
		Body Weight (kg)									
Dosing Interval	**Baseline IgE (IU/mL)**	**20-25**	**>25-30**	**>30–40**	**>40–50**	**>50–60**	**>60–70**	**>70–80**	**>80–90**	**>90-125**	**>125-150**
q4wks	≥ 30–100	75	75	75	150	150	150	150	150	300	300
	>100–200	150	150	150	300	300	300	300	300	225	300
	>200–300	150	150	225	300	300	225	225	225	300	375
	>300–400	225	225	300	225	225	225	300	300		
	>400–500	225	300	225	225	300	300	375	375		
	>500–600	300	300	225	300	300	375				
	>600–700	300	225	225	300	375					
q2wks	>700–800	225	225	300	375						
	>800–900	225	225	300	375						
	>900–1000	225	300	375							
	>1000–1100	225	300	375							
	>1100–1200	300	300								
	>1200–1300	300	375								

Do not dose

Cells added over and above the US Package Insert

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Supplement Appendix Table 3: Subgroup Analyses on participants sensitized and exposed to German cockroach

	Cockroach sensitized and Exposed *	Effect Size (95%CI) †	Percent Reduction	P	Interaction P
Symptom days (no. of days / last 2 wks) ‡	No	-0.4 (-0.7, -0.1)	20.5	0.02	0.06
	Yes	-1.1 (-1.8, -0.4)	48.5	0.001	
Inhaled glucocorticoids (μg)	No	-91 (-164, -17)	11.9	0.02	0.03
	Yes	-284 (-444, -124)	32.9	<0.001	
≥ 1 Exacerbations §	No	1.7 (1.2, 2.4)	38.4	<0.01	0.06
	Yes	3.7 (1.7, 8.1)	71.2	<0.001	

***** Cockroach sensitized and exposed is defined as those participants that have both that were both cockroach sensitized (≥3 mm skin test response) and exposed (Bla g 1 in house dust ≥2 U/g).
† Difference for symptoms days and inhaled glucocorticoids, odds ratios for exacerbations
‡ Symptom days is the largest of the following variables reported over the previous 2 weeks: (1) number of days with wheezing, chest tightness, or cough; (2) number of nights of sleep disturbance; (3) number of days when activities were affected. This symptom scale ranges from 0 to 14 days per 2 weeks.
§ An exacerbation was defined as a prednisone burst or a hospitalization

Supplement Appendix Text 1: Subgroup Analyses for the Inner City Asthma Consortium ICATA Manuscript

Subgroup analyses can sometimes create unique problems for randomized clinical trials such as the reduced statistical power due to smaller sample sizes or increased likelihood of making a Type I error as a result of multiple comparisons. In order to minimize these concerns, we employed a conservative approach to subgroup analysis as described in the publication by Wang, et al.[1]

All subgroup analyses were pre-specified before examination of the data. The subgroup analyses were limited to two demographic characteristics (Age and Body Mass Index); three measures of atopic status (cockroach sensitivity and exposure, dust mite IgE, and total IgE); and finally two measures of asthma severity (step level at randomization and one or more unscheduled asthma urgent care visits in the past year). Each of these factors has been found to be an important determination of asthma morbidity in prior studies by our group. Three outcomes were examined for each of these subgroups (symptoms, asthma exacerbations and inhaled glucocorticoids use).

Secondly, we employed the recommended statistical method for assessing the heterogeneity of omalizumab effect among the subgroups using a statistical test for interaction, adjusting for the pre specified baseline characteristics described in the protocol. Once an interaction was determined to be nominally significant we reported the quantitative effect of omalizumab with confidence intervals (not p-values).

Our finding that the effects of omalizumab were greatest on the cockroach sensitive and exposed group substantiates this as an important sub-group which was first identified in 1997 by Rosenstreich, et al.[2]. The importance of this subgroup was further substantiated by demonstrating the effects of reducing this allergen by Morgan, et al.[3] Understandably, subgroup analyses put one at risk for spurious findings. We have not corrected for multiple comparisons in these pre-specified subgroup analyses, but we believe the consistency of the omalizumab effect with respect to cockroach sensitivity and exposure on these three independent end points is compelling. In addition to the consistency of the results in this study, the history of consistency of this relationship of sensitivity and exposure to cockroach in our prior inner-city asthma studies, and among other research groups, which suggest the findings to be non-spurious.

We feel that we have reported the results of the subgroup analyses transparently and according to the recommendations provided by Wang, et al.[1]

References:

1. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med 2007; 357:2189-94.

2. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997; 36:1356-63.

3. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004; 351:1068-80.